PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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Roche Diagnostics GmbH
Patent Department Penzberg

ASK	30. Mai 2005			WN
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220 22398-WO-BUR

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/001243	08.02.2005	10.02.2004

International Patent Classification (IPC) or both national classification and IPC
C12Q1/70

Termin 1
31. 08. 2005 mit.

Applicant
ROCHE DIAGNOSTICS GMBH

1. This opinion contains indications relating to the following items: (21. 07. 05

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Termin 2
10. 12. 2005 mit.
(01. 11. 05)

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,6,7,8,10,12,14,16-23
	No:	Claims	1,2,4,5,9,11,13,15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Documents

The following documents are referred to in this communication:

D1: WO 99/28439 A (ASSIST PUBL HOPITAUX DE PARIS ; AUGUSTE VERONIQUE (FR); GARBARG CHENON) 10 June 1999 (1999-06-10)

D2: SCHMIDT I ET AL: "Parvovirus B19 DNA in plasma pools and plasma derivatives." VOX SANGUINIS. NOV 2001, vol. 81, no. 4, pages 228-235

D3: HARDER T C ET AL: "New LightCycler PCR for rapid and sensitive quantification of parvovirus B19 DNA guides therapeutic decision-making in relapsing infections" J CLIN MICROBIOL, vol. 39 (12), 2001, p. 4413-4419

2 NOVELTY

The document D1 discloses:

2.1 A method for the detection of a target nucleic acid comprising the nucleic acid sequence of parvovirus B19 in a sample comprising the steps of (a) providing a sample suspected to contain the target nucleic acid (b) providing a pair of primers comprising a first and a second primer whereby the first primer consists of at least contiguous 12 nucleotides of a nucleic acid sequence selected from the nucleic acid sequences SEQ ID NO: 2, and whereby the second primer consists of at least contiguous 12 nucleotides of a nucleic acid sequence selected from the nucleic acid sequences SEQ ID NO: 3 or 4; (c) amplifying the target nucleic acid, (d) detecting the amplified target nucleic acid of step (c) (Example 4: p. 17-18; SEQ ID NO: 12, 106 (first primer) SEQ ID NO: 14, 15 (second primer)).

2.2 A method according to claim 1 wherein the fist primer consists of at least 12 contiguous nucleotides of a nucleic acid sequence selected from the nucleic acid sequences SEQ ID NO: 6, 7 (Example 4: p. 17-18; SEQ ID NO: 11, 12, 106, 121)

and wherein the second primer consists of at least 12 contiguous nucleotides of a nucleic acid sequence selected from the nucleic acid sequences SEQ ID NO: 8 or 9 (Example 4: p. 17-18; SEQ ID NO: 14, 15).

2.3 A method for the detection of a target nucleic acid comprising the nucleic acid sequence of parvovirus B19 in a sample comprising the steps of (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of primers comprising a first and a second primer, (c) amplifying the target nucleic acid, (d) contacting the sample with a probe under conditions for binding the probe to the target nucleic acid (e) detecting the binding product between the target nucleic acid and the probe as an indication of the presence of the target nucleic acid characterized in that the first primer consists of at least 12 contiguous nucleotides of a nucleic acid sequence selected from the nucleic acid sequences SEQ ID NO: 2 (Example 4: p. 17-18; SEQ ID NO: 12, 14, 106) and in that the second primer consists of at least 12 contiguous nucleotides of a nucleic acid sequence selected from the nucleic acid sequences SEQ ID NO: 3 or 4 (Example 4: p. 17-18; SEQ ID NO: 15), and/or the probe consists of at least 12 contiguous nucleotides of the nucleic acid sequence SEQ ID NO: 5 (Example 4: p. 17-18; SEQ ID NO: 13, 107).

2.4 The method according to claim 4 wherein the probe carries a label (Example 4: p. 18, l. 23-28).

2.5 The method according to any of the claims 4, 5 wherein the target nucleic in step c) is amplified with a template-dependent DNA polymerase (Example 4, p. 17, l. 30-31).

2.6 A method according to any of the claims 4, 5, 9, wherein the probe consists of at least 12 contiguous nucleotides of the nucleic acid sequence SEQ ID NO: 10 or a complementary sequence thereof (Example 4: p. 17-18; SEQ ID NO: 13, 58, 107).

2.7 A method according to any of the claims 4, 5, 9, 11 wherein the first primer consists of at least 12 nucleotides of a nucleic acid sequence selected from the nucleic acid sequences SEQ ID NO: 6 or 7 and the second primer consists of at least 12 nucleotides of a nucleic acid sequence selected from the nucleic acid sequences SEQ ID NO: 8 or 9 (Example 4: p. 17-18: SEQ ID NO: 11, 12, 14,15, 106, 107).

2.8 A method according to any of the claims 4, 5, 9, 11, 13 wherein thc primer and/or the probe comprise a modified nucleotide or a non-nucleotide compound (Example 4: p. 18, l. 23-28).

The subject-matter of claims **1, 2, 4, 5, 9, 11, 13, 15** is therefore not new (Article 54(1) and (2) EPC) over **D1**.

3 INVENTIVE STEP

3.1 The subject-matter, which appears to be the basis of the present invention comprises the oligonucleotides specific for the NS-1 gene of the parvovirus B19, which are not known from the prior art cited (cf. D1 and D2):
An oligonucleotide with a nucleic acid sequence selected from SEQ ID NOs. 10 - 17 or a complementary sequence thereof.

3.1.1 Document D1, which is considered to represent the most relevant state of the art, discloses a method according to claim 1 or claim 4 of the present application (see above), from which the subject-matter of the present invention differs in that the sample is contacted with a different pair of primers for the amplification step and a different probe for the detection step.

3.1.2 The problem to be solved by the present invention may therefore be regarded as the provision of alternative oligonucleotides for the detection of parvovirus B19 in a sample by amplification with a primer pair followed by probe(s) hybridization.

3.1.3 The solution proposed in the present application cannot be considered as involving an inventive step (Art. 33(3) PCT) for the following reasons:
Oligonucleotides of the same region of the NS-1 protein of the parvovirus B19 as the oligonucleotides of the present invention are already disclosed the prior art and have already been used as amplification primers and as hybridization probes (cf. D1: Example 4; SEQ ID NO: 12-15, 106, 107, 121; cf. D2: p. 229,, col. 2, par. 3; see above).
The oligonucleotides disclosed in D1 even overlap with, include or are included in the oligonucleotides of the present application (cf. D1: SEQ ID NO. 15 overlaps with or includes SEQ ID NOs. 4, 16, 17 of the present application; SEQ ID NOs. 11 and 121 overlap or include SEQ ID NOs. 6, 12, 13, 14, 15 of the present application; SEQ ID NO. 12 is included in SEQ ID NO. 7 of the present application; SEQ ID NO. 14 is included in SEQ ID NO. 8 of the present application; SEQ ID NOs. 13 and 107 overlap with or include SEQ ID NOs. 10 and 11 of the present application).
Similarly, the primers and probes disclosed in D2 also overlap with the primers and probes of the present application (cf. D2: primer TP1 is included in SEQ ID NO: 2

and overlaps with SEQ ID NOs. 7, 13, 14, 15 of the present application; primer TP2 overlaps with SEQ ID NO: 3 of the present application; the probe overlaps with SEQ ID NOs. 2, 5, 7, 10, 11, 13, 14, 15 of the present application).
Therefore, the prior art available would already direct the person skilled in the art to that particular region of the NS-1 gene of parvovirus B19 for the selection of further parvovirus B19-specific primers or probes. Hence, the selection of an oligonucleotide with a nucleic acid sequence consisting of SEQ ID NO. 10, 11, 12, 13, 14, 15, 16 or 17, merely represents an arbitrary selection of an oligonucleotide from a number of equally likely alternatives, which does not involve inventive activity.
Such a selection would only be regarded as inventive if the selected oligonucleotide presented unexpected effects or properties in relation to the rest of the possible choices. However, the oligonucleotides with a nucleic acid sequence consisting of SEQ ID NO. 10 - 17 do not appear to have such unexpected properties.

Therefore, the subject-matter of independent claims **18, 21, 22** and dependent claims **3, 12** and **14** cannot be considered as inventive in the sense of Art. 33(3) PCT.

3.2 The oligonucleotides with a nucleic acid sequence consisting of SEQ ID NO. 10 - 17 cannot be considered as inventive (see above paragraph 3.1).
Therefore, a pair of primers comprising a first primer selected from SEQ ID. N: 12 to 15 and a second primer selected from the complementary sequence of SEQ ID. NO: 16 to 17 and/or a kit comprising said pair of primers or an oligonucleotide with a nucleic acid sequence consisting of SEQ ID NO. 10 - 17 cannot be considered as inventive (Art. 33(3) PCT), either, as the regrouping of known or non-inventive reagents for a known or obvious experiment into the form of a kit does not require inventive activity for the person skilled in the art.
Hence, the subject-matter of independent claims **20** and **23** cannot be considered as being inventive in the sense of Art. 33(3) PCT.

3.3 Dependent claims **6 - 8, 10, 16, 17** and **19** do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, see documents D1, D2 and D3 and the corresponding passages cited in the search report.

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